# Emicizumab (haemophilia A)

## Benefit assessment according to §35a SGB V[1]

**EXTRACT**

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Emicizumab (Hämophilie A) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**Patient and family involvement**

The questionnaire on the disease and its treatment was answered by Tobias Becker and Dragana Mitrovic.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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# Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

# I List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug emicizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 February 2023.

### Research question

The aim of this report is to assess the added benefit of emicizumab in comparison with the appropriate comparator therapy (ACT) for routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of emicizumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype[b] | Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis |
| a. Presented is the ACT specified by the G-BA.<br>b. It is assumed that the patient population in the present therapeutic indication is haemophilia patients requiring factor VIII substitution.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. A minimum study duration of 24 weeks was defined for the derivation of the added benefit.

### Results

Concurring with the company, the check of completeness of the study pool found no randomized controlled trial (RCT) of direct comparison of emicizumab versus the ACT. Among the further investigations, the company identified the single-arm study HAVEN 6 (BO41423) for emicizumab and used this study to derive the added benefit. The HAVEN 6 study is unsuitable for the derivation of an added benefit because, as a single-arm study, it does not

permit a comparison with the ACT. The company did not conduct any further information retrieval for the ACT.

**Results on added benefit**

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of emicizumab in comparison with the ACT; an added benefit is therefore not proven.

## Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of emicizumab.

Table 3: Emicizumab – probability and extent of added benefit

| Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype[b] | Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population in the present therapeutic indication is haemophilia patients requiring factor VIII substitution.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

## I 2 Research question

The aim of this report is to assess the added benefit of emicizumab in comparison with the ACT for routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of emicizumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| Routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype[b] | Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis |
| a. Presented is the ACT specified by the G-BA.<br>b. It is assumed that the patient population in the present therapeutic indication is haemophilia patients requiring factor VIII substitution.<br>ACT: appropriate comparator therapy; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. A minimum study duration of 24 weeks was defined for the derivation of the added benefit. This concurs with the company's inclusion criteria.

## I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on emicizumab (status: 25 January 2023)
- bibliographical literature search on emicizumab (last search on 2 January 2023)
- search in trial registries/trial results databases for studies on emicizumab (last search on 27 December 2022)
- search on the G-BA website for emicizumab (last search on 10 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on emicizumab (last search on 2 March 2023); for search strategies, see I Appendix A of the full dossier assessment

**Direct comparison**

Concurring with the company, the check of completeness of the study pool found no RCT of direct comparison of emicizumab versus the ACT.

**Further investigations**

As the company identified no studies for a direct comparison, it conducted an information retrieval for further investigations with emicizumab. In this information retrieval, it identified the HAVEN 6 study (BO41423) [3] and used this study to derive the added benefit.

The HAVEN 6 study is a single-arm study, which included patients of all age groups with mild (factor VIII activity > 5% and < 40%) or moderate (factor VIII activity ≥ 1% and ≤ 5%) congenital haemophilia A without factor VIII inhibitors with a need for prophylaxis based on investigator assessment. According to the case report form of the HAVEN 6 study, the following reasons could be selected (multiple answers possible): history of frequent bleeding, history of frequent joint bleeding, history of severe bleeding (e.g. intracranial bleeding), physically active lifestyle, prevention of traumatic bleeding, other. In the HAVEN 6 study, history of frequent bleeding (57%) and history of frequent joint bleeding (44%) were the most commonly reported reasons for the therapeutic indication of prophylaxis.

More than half of the patients were already receiving routine prophylaxis with factor VIII preparations before enrolment. Treatment in the study included the routine prophylaxis with emicizumab with an initial dosing of 3 mg/kg per week for the first 4 weeks, and starting from week 5, with a maintenance dosing of either 1.5 mg/kg once a week, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks. The planned treatment duration was at least 52 weeks. The primary

outcome of the study was treated bleeds, operationalized as annualized bleed rate. In its dossier, the company presented analyses for the subpopulation of the HAVEN 6 study with moderate haemophilia A.

The HAVEN 6 study is unsuitable for the derivation of an added benefit because, as a single-arm study, it does not permit a comparison with the ACT. In addition, the company stated that there were no data on routine prophylaxis with coagulation factor VIII preparations in the therapeutic indication to be assessed and that therefore no direct or indirect comparison was possible. The company conducted no information retrieval for the ACT, however. The completeness of the study pool for further investigations was not checked.

## I 4 Results on added benefit

No suitable data are available to assess the added benefit of emicizumab in comparison with the ACT for routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype. There is no hint of an added benefit of emicizumab in comparison with the ACT; an added benefit is therefore not proven.

## I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of emicizumab in comparison with the ACT is summarized in Table 5.

Table 5: Emicizumab – probability and extent of added benefit

| **Therapeutic indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors who have moderate disease (factor VIII ≥ 1% and ≤ 5%) with severe bleeding phenotype[b] | Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population in the present therapeutic indication is haemophilia patients requiring factor VIII substitution.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit for emicizumab.

The G-BA decides on the added benefit.

## I 6 References for English extract

Please see full dossier assessment for full reference list.

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*The full report (German version) is published under https://www.iqwig.de/en/projects/a23-10.html.*